Claims

1. A process for the preparation of a substantially pure amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, wherein the procedure comprises the steps of:

a) dissolving 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A material in

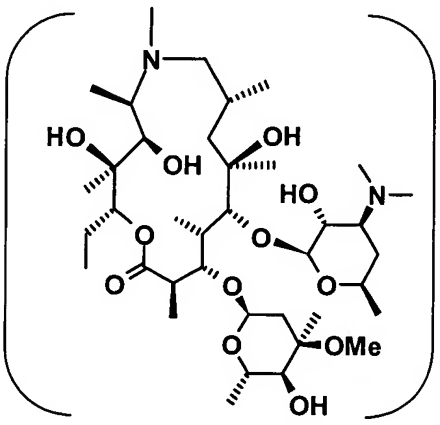
(1) an organic solvent that is water-miscible or water-immiscible,

(2) a mixture of organic solvents,

(3) a mixture of organic solvents and water, or

(4) a mixture of water and at least one inorganic or organic acid;

b) crystallizing an orthorhombic isostructural pseudopolymorph of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A of the general Formula I



$\times [H_2O] \times [S]$ **I**

wherein S is a water-miscible or water-immiscible organic solvent,

the pseudopolymorph being characterized by the orthorhombic space group $P2_12_12_1$ and average unit cell parameters comprising:

crystal axis lengths of a = 8.2 to 9.7 Å, b = 11.5 to 13.5 Å, and c = 44.5 to 47.0 Å, and

angles between the crystal axes of $\alpha = \beta = \gamma = 90°$, from the solution thus prepared;

c) isolating the orthorhombic isostructural pseudopolymorph of the general Formula I; and

d) converting the orthorhombic isostructural pseudopolymorph of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A of the general Formula I to a subtantially pure amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A.

2. The process of claim 1, wherein the 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A material dissolved in step (a) is (i) a crystalline 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A in crude or purified form, (ii) an amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A in crude or purified form, (iii) solvates or hydrates of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, whether in crude or purified form, or (iv) a native solution of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A formed during the last step of its syntheses from any one of its last intermediates.

3. The process of claim 2, wherein the 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A utilized to prepare a substantially pure amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, dissolved in step (a) is a crude 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A in any of its known forms and having a purity less than the pharmaceutically acceptable purity.

4. The process of claim 2, wherein the native solution of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A used for preparing a substantially pure amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, in the solvent dissolved in step (a) is a solution of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A formed in the native solvent during the last step of its syntheses from any one of its last intermediates.

5. The process of claim 2, wherein the native solution of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A used for preparing substantially pure amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A dissolved in step (a) is a solution of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, formed in the native solvent during the last step of its syntheses from 9-deoxo-9a-aza-9a-homoerythromycin A as its last intermediate.

6. The process of claim 2, wherein the 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A dissolved in step (a) is in the form of a dispersion of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A and the 9-deoxo-9a-aza-9a-homoerythromycin A intermediate in a native solvent used in the last step of a synthesis of crude 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A.

7. The process of claim 4, wherein the native solvent in the native solution is selected from the group consisting of haloalkanes having 1 or 2 carbon atoms, esters of acetic acid with a C_2-C_4 lower alkyl group, monohydroxyl C_2-C_4 alkanols, C_1-C_4 ketones, linear or cyclic ethers, aromatic or substituted aromatic compounds, and mixtures thereof.

8. The process of claim 2, wherein the 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A dissolved in step (a) is amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A; a crystalline anhydrous, monohydrate, dihydrate or solvate of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A; or an orthorhombic isostructural pseudopolymorph of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A of Formula I.

9. The process of claim 2, wherein the 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A dissolved in step (a) is of pharmaceutically acceptable purity.

10. The process of claim 1, wherein step (a) is conducted at a temperature of from about 30°C to about 100°C.

11. The process of claim 1, wherein the organic solvent in which the 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A material is dissolved in step (a) is selected from the group consisting of linear or branched C_1-C_5 alkanes, C_5-C_8 cycloalkanes, linear or branched C_1-C_6 alkanols, C_5-C_8 cycloalkanols, arylalkanols, C_2-C_4 diols, triols, C_1-C_4 ethers, C_3-C_5 ketones, C_1-C_4 alkyl estersof C_1-C_4 alkanoic and hydroxyalkanoic acids, amides, ureas, C_2-C_4 nitriles, sulfoxides, sulfones, heterocyclic amines, lactams, and mixtures thereof.

12. The process of claim 1, wherein the inorganic of acid is selected from the group consisting of hydrochloric acid, sulfuric (VI) acid, sulfuric (IV) acid, and mixtures thereof.

13. The process of claim 1, wherein the organic acid is selected from the group consisting of formic acid, acetic acid, propionic acid, citric acid, tartaric acid, maleic acid, oxalic acid, chloroacetic acid, benzoic acid, methanesulfonic, *p*-toluenesulfonic acid, and mixtures thereof.

14. The process of claim 1, wherein the orthorhombic isostructural pseudopolymorph of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A is crystallized in step (b) by controlled cooling of the solution containing the 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A at temperatures of from about 80°C to about -10°C.

15. The process of claim 1, wherein the orthorhombic isostructural pseudopolymorph of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A is crystallized in step (b) isothermally at temperatures of from about 25°C to about 60°C, by standing or mixing the solution formed in step (a) in a water-miscible or water-immiscible organic solvent at said isothermal conditions.

16. The process of claim 1, wherein the orthorhombic isostructural pseudopolymorph of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A is crystallized in step (b) isothermally at a temperature of about 25°C to about 60°C by saturating the solution formed in step (a) in a water-miscible or water-immiscible organic solvent with an organic counter-solvent until the solution becomes slightly turbid.

17. The process of claim 16, wherein the organic counter-solvent is water.

18. The process of claim 1, wherein the orthorhombic isostructural pseudopolymorph of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A is crystallized in step

(b) by neutralizing the aqueous acidic solution of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A formed in step (a) at temperatures of about 80°C to about -10°C.

19. The process of claim 1, wherein the orthorhombic isostructural pseudopolymorph of general Formula I is crystallized in step (b) by neutralizing an acidic solution of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A material from step (a) with one or more inorganic or organic base.

20. The process of claim 18, wherein the inorganic base is a alkali or alkali-earth metal hydroxide, oxide or carbonate, or an ammonia solution.

21. The process of claim 19, wherein the organic base is an organic amine.

22. The process of claim 21, wherein the organic amine is selected from the group consisting of trimethylamine, triethylamine, piperidine, 3-methylpyridine, piperazine, triethanolamine, and ethylene diamine.

23. The process of claim 19, wherein the organic base is a quartenary organic hydroxide.

24. The process of claim 23, wherein the quartenary organic hydroxide is selected from the group consisting of tetramethyl ammonium hydroxide, tetraethyl ammonium hydroxide, and tetrabutyl ammonium hydroxide.

25. The process according to claim 1, wherein the orthorhombic isostructural pseudopolymorph of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A of Formula I is added to the solution in step (b) in an amount of from about 0.01 to about 5.0 wt. % based on the amount of the starting 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, to seed crystallization of the orthorhombic isostructural pseudopolymorph of the general Formula I therein.

26. The process of claim 1, wherein the orthorhombic isostructural pseudopolymorph of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A of Formula I is isolated in step (c) by:

(i) separating the pseudopolymorph from the solution formed in step (a);

(ii) washing the obtained product with solvents (1), (2) or (3) used in step (a), at temperatures of from about -10°C to about 40°C; and

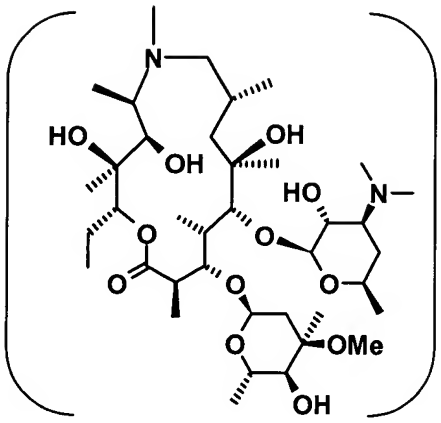
(iii) drying the washed product under atmospheric pressure at temperatures of from about 20°C to about 80°C, or under reduced pressures of from about 2 kPa to about 80 kPa.

27. The process of claim 1, wherein the orthorhombic isostructural pseudopolymorph of Formula I is transformed in step (d) to a substantially pure stable amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A by lyophilizing or further drying the orthorhombic isostructural pseudopolymorph at reduced pressures from about 0.01 kPa to about 80 kPa and temperatures of from about -100°C to about 100°C.

28. The process of claim 1, wherein the substantially pure amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A prepared in step (d) is characterized by the non-existence of isolated peaks in powder diffractogram, by a water content of from bout 1.5 to about 2.5%, a granular habit, a specific dissolution profile as well as a specific intrinsic dissolution rate (IDR) at 37°C.

29. The substantially pure orthorhombic isostructural pseudopolymorph of Formula I, prepared by the process of claim 1.

30. A substantially pure orthorhombic isostructural pseudopolymorph of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A of the general formula I



× [H_2O] × [S] I

wherein S represents a water-miscible or water-immiscible organic solvent, characterized by the orthorhombic space group $P2_12_12_1$, and having average unit cell parameters of

a = 8.2 to 9.7 Å,

b = 11.5 to 13.5 Å,

c = 44.5 to 47.0 Å, $\alpha = \beta = \gamma = 90°$,

wherein a, b and c represent the crystal axes lengths, and α, β and γ represent the angles between the crystal axes.

31. The substantially pure orthorhombic isostructural pseudopolymorph of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A of claim 29 selected from the group of pseudopolymorphs (Ia) – (Id) set forth below, wherein S in Formula I and the average unit cell parameters, i.e. the crystal axes lengths a, b and c, and angles α, β and γ between the crystal axes of the crystal structure are:

(Ia) S = 1,4-dioxane, and at 22°C:

a = 8.8290(20) Å,

b = 12.167(2) Å,

c = 45.853(8) Å, and

$\alpha = \beta = \gamma = 90°C$,

(Ib) S = *tert*-butanol and, at -173°C:

a = 8.84240(10) Å,
b = 11.91730(10) Å,
c = 45.9493(6) Å, and
$\alpha = \beta = \gamma = 90°C$

(Ic) S = methyl *tert*-butyl ether and, at 22°C:
a = 8.92080(10) Å,
b = 12.34770(10) Å,
c = 45.71900(10) Å, and
$\alpha = \beta = \gamma = 90°C$,

(Id) S = cyclohexane and, at 22°C:
a = 8.8573(23) Å,
b = 12.520(7) Å,
c = 45.624(11) Å, and
$\alpha = \beta = \gamma = 90°C$.

32. Substantially pure amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A prepared by the process of Claim 1.

33. The substantially pure amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A prepared by the process of Claim 1, characterized by the non-existence of isolated peaks in a powder diffractogram, a water content from about 1.5 to about 2.5%, a granular habit, a specific dissolution profile as well as a specific intrinsic dissolution rate (IDR) at 37°C.

34. A pharmaceutical composition comprising substantially pure amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A prepared by the process of claim 1, and one or more pharmaceutically acceptable excipients.

35. A pharmaceutical composition for oral, rectal, parenteral, transdermal, buccal, nasal, sublingual, subcutaneous or intravenous application, comprising substantially pure amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, prepared by the process of claim 1, and one or more pharmaceutically acceptable excipients.

36. A method for treating bacterial and protozoal infections, and inflamation-related diseases in humans and animals, comprising administering to a human or animal in need thereof the pharmaceutical composition of claim 34.